REMARKS

Status of the Claims

Claims 1, 3-6, 12, and 14-31 are currently pending in the present application. Claims 3, 6, 12, and 14-16 are withdrawn as directed to a non-elected invention. Claims 17-31 are new. Claims 2, 7-11, and 13 are canceled without prejudice or disclaimer. Claim 1 is amended without prejudice or disclaimer. Examined claim 4 and withdrawn claims 3 and 6 are amended to depend solely on pending claim 1. Withdrawn claims 12 and 16 are also amended to depend solely on pending claim 5. Applicants reserve the right to claim any canceled subject matter in one or more divisional or continuation applications.

Support for amended claim 1 and new claims 21-23 is found throughout the application as originally filed, including, *e.g.*, original claim 2, on page 24, paragraph 4, pages 24-25, bridging paragraph, page 25, paragraph 1, and page 27, paragraph 1. Support for new claims 17-20 and 24-31 is found throughout the specification as originally filed, including, *e.g.*, in original claim 2 and in SEQ ID. NOS: 1-3 as originally filed.

Issues Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1-2 and 4-5 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement, *see* Office Action, pages 2-5. Specifically, the Examiner states that the present application allegedly fails to describe a correlation between the structure of the disclosed sequences and the corresponding functional activity, *see* Office Action, pages 3-4. For the reasons set forth below, Applicants respectfully traverse.

In order to comply with the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. An Applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics,

which provide evidence that Applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Enzo Biochem*, 323 F.3d at 964, 63 USPQ2d at 1613. Information which is well known in the art need not be described in detail in the specification. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

Independent claim 1, as amended, is directed to a DNA participating in biological transformation of a macrolide compound 11107B represented by the formula (I), as described, into a 16-position hydroxy macrolide compound represented by the formula (II), *i.e.* compound 11107D, as described, the DNA being an isolated and pure DNA comprising a DNA encoding a protein having a 16-position hydroxylating enzymatic activity, which is characterized by the following (a), (b), or (c): the DNA being an isolated and pure DNA comprising a DNA encoding a protein having 16-position hydroxylating enzymatic activity which is characterized by the following (a), (b), or (c): (a) a DNA encoding a protein having the enzymatic activity to hydroxylate the 16-position of the macrolide compound 11107B, wherein the DNA is selected from the group consisting of (1) a continuous nucleotide sequence from base 1322 to base 2548 of SEQ ID NO: 1; (2) a continuous nucleotide sequence from base 420 to base 1604 of SEQ ID NO: 2; and a continuous nucleotide sequence from base 172 to base 1383 of SEQ ID NO: 3; (b) a DNA which has a nucleotide sequence having 90% or more identity with the DNA described in (a); (c) a DNA encoding a protein having the same amino acid sequence as the protein encoded by the DNA described in (a) or (b) though it does not have 90% or more identity with the DNA described in (a) because of the degeneracy of a gene codon.

New independent claim 22, as amended, is directed to (a) a DNA encoding a protein, wherein the DNA is selected from the group consisting of (1) a continuous nucleotide sequence from base 1322 to base 2548 of SEQ ID NO: 1; (2) a continuous nucleotide sequence from base 420 to base 1604 of SEQ ID NO: 2; and a continuous nucleotide sequence from base 172 to base 1383 of SEQ ID NO: 3; (b) a DNA which has a nucleotide sequence having 90% or more identity with the DNA described in (a); or (c) a DNA encoding a protein having the same amino

acid sequence as the protein encoded by the DNA described in (a) or (b) though it does not have 90% or more identity with the DNA described in (a) because of the degeneracy of a gene codon.

Applicants submit that independent claim 1, as amended, and new claim 22 comply with the written description requirement. A person of ordinary skill in the art would have been able to readily visualize those variants having at least 90% identity to the nucleotide bases, or the amino acid sequences encoded by the nucleotide bases, which are described in part (a) of claim 1 or part (a) of claim 22. In addition, a person of ordinary skill in the art at the time of the invention also would have been able to readily visualize the 10% of the nucleotide bases that could have been substituted to derive variant nucleic acids, which encode for amino acid sequences that retain the described hydroxylating enzyme activity as described in amended claim 1.

The present application teaches that the sequences specified in the instant claims contain ORFs PsmA, BpmA and TpmA that show high identity to cytochrome P450, *see e.g.*, page 52, paragraph 1, page 68, paragraph 2, and page 77, paragraph 3 in the originally filed application. Accordingly, the claimed sequences belong to a well-known family of nucleic acids encoding polypeptides, which were understood to contain conserved amino acid residues that correlate with the described enzymatic activity.

For example, a person of ordinary skill in the art at the time of the invention was well-aware that cytochrome P450 sequences include amino acids, which are conserved among phylogenetically diverse species including humans and bacteria, *see e.g.*, Exhibit A, enclosed, (*i.e.*, Gotoh, *The Journal of Biological Chemistry*, 267, 1992, 83-89,) page 84, right column, results section. Exhibit A further describes that, after aligning fifty-one P450 family 2 (CYP2) sequences, including those from humans with 8 bacterial cytochrome P450 sequences, "*the human CYP2 profiles clearly resemble the bacterial profiles*", with the exception of a few described gaps, *see* Exhibit A, page 34, right column results section, lines 11-14, *emphasis added.*

Exhibit A further teaches that the substrate recognition sites may be predicted in human CYP2 proteins from bacterial P450 proteins. For example, Exhibit A teaches that the substrate recognition region of a human P450 can be predicted from the crystalline structure of bacterial cytochrome P450 101A. X-ray crystallography of substrate-bound forms of bacterial

cytochrome P450 showed that a substrate, camphor, interacts with protein residues dispersed in several separate loci in the primary structure, *see* page 85, right column paragraph 1. The location of the corresponding substrate-binding residues in human may be predicted from an alignment between human CYP2 and bacterial P450s, *see* Figure 3, and page 86 of Exhibit A. Accordingly, an ordinary artisan can similarly envision the substrate binding regions of the instant novel cytochrome P450 sequences from known cytochrome P450 sequences.

Exhibit B, (*i.e.*, Werck-Reichhart *et al.*, *Genome Biology*, 2000, 1: 3003.1-3003.9), further teaches that cytochrome P450 proteins are highly conserved at the core of the protein around the heme, which reflects a common mechanism of electron and protein transfer and oxygen activation. Based upon the foregoing, it is evident to an ordinary artisan that the catalytic domain within a given cytochrome P450 polypeptide sequence may be predicted from locating the corresponding domains within a P450 sequence, for which a function has previously been identified, *see* page 3003.3, and Figure 1(b), Exhibit B.

Exhibit C, (*i.e.* O'Keefe *et al.*, 1991, *Molecular Microbiology*, 5:2099-2105), shows a family of actinomyces CYP105 proteins containing PsmA, BpmA and TpmA. Actinomyces cytochrome P450 protein sequences are depicted at Figure 2 on page 2102 and described on page 2103, right hand column, paragraph 1. Exhibit C states that distinct patches of residues are conserved among the amino acid sequences within *Streptomyces* and those with clearly defined relationships to function have been described at length, *see* Figure 2, Exhibit C and page 2104, left column, top.

As noted above, the prior art teaches substrate binding domains and catalytic domains for cytochrome P450 sequences. Accordingly, an ordinary artisan can envision where such regions are located within the instantly claimed cytochrome P450 sequences with, *e.g.*, the aid of alignment software and/or software that describes secondary and/or tertiary structure, which was well-known in the art at the time of the invention. Further, nucleic acid substitutions encoding for amino acid substitutions outside of the two functional domains, or outside of amino acids that are not conserved, are unlikely to greatly affect the described enzymatic activity. In addition, each of the claimed sequences described in part (a) of claim 1 share approximately 70% to 80% identity with each other and share the described hydroxylating enzymatic activity. Accordingly,

an ordinary artisan recognizes that variants of the described sequences, even those sharing less than the at least 90% identity as claimed, are capable of retaining the described enzymatic activity.

Based upon the foregoing, Applicants submit that the disclosure regarding SEQ ID NOS. 1-3 combined with the knowledge in the art would have put one in possession of the genus of nucleic acids having 90% identity to the sequences specified in the instant claims having the described functional activity. Accordingly, Applicants submit that the instant claims comply with the written description requirement and respectfully request withdrawal of the rejection.

Issues Under 35 U.S.C. § 102(b), Anticipation

Claims 1-2 and 4-5 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Publication No. WO 03/040370 to Nakajima *et al.* as evidenced by the corresponding English language application U.S. Publication No. 2005/0084859 to Nakajima *et al.*, ("Nakajima"), *see* Office Action, pages 5-6. Specifically, the Examiner states that SEQ ID NO. 237 of the Nakajima document is over 80% identical to nucleotides 1322 to 2548 of SEQ ID NO. 1, *see* Office Action, page 5.

The present claims are directed to sequences having at least 90% identity to bases 1322-2548 of SEQ ID NO. 1. Accordingly, Nakajima et al. does not anticipate the instant claims and the rejection should be withdrawn.

CONCLUSION

In view of the above amendment and remarks, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____ # 42,874

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